Original Research

Preclinical and clinical evidence of activity of pazopanib in solitary fibrous tumour

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Abstract **Background:** To explore the activity of pazopanib in solitary fibrous tumour (SFT). **Patients and methods:** In a preclinical study, we compared the activity of pazopanib, sorafenib, sunitinib, regorafenib, axitinib and bevacizumab in a dedifferentiated-SFT (DSFT) xenotransplanted into Severe Combined Immunodeficiency (SCID) mice. Antiangiogenics were administered at their reported optimal doses when mean tumour volume (TV) was 80 mm^3. Drug activity was assessed as TV inhibition percentage (TVI%). From May 2012, six consecutive patients with advanced SFT received pazopanib, on a national name-based programme. In one case sunitinib was administered after pazopanib failure.

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Results: In the xenograft model, pazopanib showed the lowest antitumour activity (21%TVI), while regorafenib was the most active (95%TVI). Sorafenib, bevacizumab, sunitinib were markedly active (78/70/65%TVI). Axitinib was marginally active (51%TVI).

In the retrospective case-series, three patients carried malignant-SFT (MSFT), three DSFT. Best Response Evaluation Criteria in Solid Tumour (RECIST) responses were: three stable disease (SD), all MSFT, three progressive disease (PD), all DSFT, corresponding to one partial response (PR), two SD, three PD by Choi criteria. Median-progression-free survival was 3 months (range 1–15). In one patient, sunitinib was started after pazopanib failure, with a response.

Conclusions: In dedifferentiated-SFT xenograft pazopanib induced a marginal antitumour activity, while regorafenib appeared the most active and promising agent. When administered in patients, pazopanib showed a modest activity in terms of tumour growth stabilisation, observed only in non-dedifferentiated cases.

1. Introduction

Pazopanib is an inhibitor of vascular endothelial growth factor receptor (VEGFR) 1–3 recently approved for treatment of non-adipocytic advanced soft tissue sarcoma (STS) after failure to front-line chemotherapy [1]. In a Phase 3 study on pazopanib in non-adipocytic STS the median progression-free survival (PFS) was 4.6 months for pazopanib compared with 1.6 months for placebo, with an overall survival (OS) of 12.5 months versus 10.7 months [2].

Very few data are available on the activity of pazopanib in solitary fibrous tumour (SFT), a rare STS sub-type [3], the sensitivity of which to antiangiogenics like sorafenib, sunitinib and bevacizumab is reported [4–9]. Antiangiogenics were shown to produce durable disease stabilisation in a proportion of patients by means of tumour responses that were mostly non-dimensional [5,6]. We already reported on the activity of pazopanib in a human high-grade dedifferentiated-SFT xenotransplanted into severe combined immunodeficiency (SCID) mice [10]. When compared to dacarbazine and temozolomide, pazopanib was less active and characterised by a short lasting cytostatic effect. Thus, we decided to expand that experiment to a broader number of antiangiogenic agents (i.e. sorafenib, regorafenib, axitinib in addition to sunitinib and bevacizumab) already applied in the clinical practice. Our findings are reported herein.

Within a name-based protocol following the results of the Phase 3 trial, we treated with pazopanib six patients affected by SFT. We report herein their outcome as well.

2. Patients and methods

2.1. Experimental model and pharmacological studies

A patient-derived human high-grade dedifferentiated-SFT xenograft model [10] was used in the study. The presence of the typical *NAB2-STAT6* rearrangement – recently described in human SFT [12] – was confirmed in xenograft by RT-PCR [10].

The xenograft model was maintained by serial sub-cutis (s.c.) passages in 6 week-old female SCID mice (Charles River, Calco, IT). Briefly, when tumours reached approximately 500 mm^3, they were removed, aseptically dissected, cut into small fragments ($3 \times 3 \times 3$ mm) and s.c. implanted in the mouse right flank. Twenty-four hours after tumour inoculum, 100 µL of Matrigel Basement Matrix (BD Biosciences) was injected intratumourally. Mice were housed in a pathogen-free facility with free access to food and water. Tumour growth was followed by biweekly measurement of tumour diameters with a Vernier caliper, and tumour volume (TV) was calculated according to the following formula: TV (mm^3) = $d^2 \times D/2$, where d and D are the shortest and the longest diameter, respectively.

2.1.1. Xenograft treatment

Treatment was started when xenotransplanted tumours were approximately 80 mm^3 (day 35). Eight mice for each group were used. Pazopanib, sorafenib, sunitinib, regorafenib and axitinib were all dissolved in 0.5% carboxymethylcellulose and delivered by oral gavage 5 days/week for 4 weeks (qd × 5d/w × 4w) × 2 after a 3-week rest at their reported optimal dose of 100/60/40/30 and 2 × 25 mg/kg, respectively. Bevacizumab was delivered intraperitoneally twice a week for 4 weeks (q3–4d/w × 4w) × 2 after a 3-week rest at its reported optimal dose of 4 mg/kg [12–16]. Control mice were treated with vehicle.

Antitumour activity was assessed as tumour volume inhibition percentage (TVI%) in treated versus control mice (TVI% = 100 − (T/C × 100) × 100, where T and C are the mean tumour volume of treated and control mice, respectively). Drug toxicity was determined as body weight loss and lethal toxicity.

The use of patient material in xenograft and all the experiments were approved by the Ethics Committee for Animal Experimentation of Fondazione IRCCS

Istituto nazionale dei tumori Milan, Italy (INT), in compliance with national and international law and policies.

2.1.2. PDGFRB, VEGFR2 and ERK1/2 expression/activation

PDGFRB expression/activation was analysed by Western blotting (WB) on 20 μg of protein lysates using anti-PDGFRB (1:1000; #4564; Cell Signaling Technology, Danvers, MA) and anti-phospho-PDGFRB (1:1000; #3166 Tyr751; Cell Signaling Technology) antibodies. Anti-actin antibody (1:2500; A2066; Sigma–Aldrich, St. Luis, MO) was used to ensure equal loading of proteins and to normalise the results.

VEGFR2 was analysed by immunoprecipitation (IP)/WB: equal amounts (1 mg) of protein lysates were precipitated by incubation with anti-VEGFR2 Sepharose bead Conjugate (#5168; Cell Signaling Technology). WB was carried-out using anti-phosphotyrosine antibody (1:3000; 05–321; Merck Millipore, Billerica, MA) to detect VEGFR2 activation. The filters were stripped and incubated with anti-VEGFR2 antibody (1:1000; #2479; Cell Signaling Technology) to evaluate VEGFR2 degree of expression.

ERK1/2 expression and activation were evaluated by WB on 20 μg of protein lysates using anti-phospho-MAPK (1:1000; #4376 Thr202/Tyr204; Cell Signaling Technology) and anti-MAPK (1:1000; #9102 p44/42; Cell Signaling Technology) antibodies. Anti-actin antibody was used to ensure equal loading of proteins and to normalise the results.

2.2. Patients

We identified six patients with metastatic SFT consecutively treated within the Italian name-based programme on pazopanib in advanced STS, open from May 2012 to May 2013. Patients were treated at INT and in other four Italian institutions. Only cases whose diagnosis was centrally confirmed by expert sarcoma pathologists (SP and APDT) are included in this study. Performance status (ECOG) ⩽ 3, adequate bone marrow and organ function, past medical history negative for deep vein thrombosis, pulmonary embolism or cerebral vascular disorder were requested.

All patients provided a written informed consent to the treatment with pazopanib. Approval by each Institutional Review Board was also required.

2.2.1. Treatment

Patients received oral pazopanib 800 mg/day (i.e. 400 mg × 2/day), continuously, until progression or toxicity. Treatment was withheld for haematologic grade (G) ⩾ 3 and for non-haematologic G ⩾ 2 adverse events (AE) as defined according to the National Cancer Institute Common Toxicity Criteria, version 3.0, and restarted after recovery to G < 2 in case of haematologic or G < 1 in case of non-haematologic.

2.2.2. Clinical assessment

Biochemistry and blood count were evaluated at baseline and monitored throughout the study period. AE were recorded. Disease status was assessed by whole body computed tomography scan (CT) and a CT of the sites of disease at baseline and repeated after 4–6 weeks of treatment, at 2–3 months, then every 3 months.

2.2.3. Efficacy assessment

All cases were centrally reviewed at INT. Response to treatment was assessed by Response Evaluation Criteria in Solid Tumour (RECIST), version 1.1, and by Choi criteria [17]. Choi criteria are based on changes in tumour size (>10% maximum diameter) and density following contrast administration on CT.

OS and PFS were estimated using the Kaplan–Meier method. Patients without evidence of progression and interrupting treatment with pazopanib for any reason were censored at the last tumour assessment. Patients alive or lost to follow-up were censored at the last contact.

2.2.4. Morphology and immunophenotype

Diagnosis was centrally reviewed according to the last World Health Organisation (WHO) classification [3]. All selected cases were positive for CD34 and STAT6. Two additional cases included in the named-base programme were excluded from this study since SFT diagnosis was not confirmed by pathologic review.

2.2.5. Role of the funding source

Glaxo Smith Kline provided pazopanib on a case by case basis, and was informed of the results. The corresponding author had the final responsibility for the decision to submit the paper for publication, and wrote the manuscript with all the other authors. The Company played no role in writing or revising the manuscript.

3. Results

3.1. Experimental model and pharmacological studies

3.1.1. Antitumour activity studies

A significant tumour growth inhibition was observed following treatment with the different anti-angiogenic agents, even if at a different extent. The only exception was pazopanib that showed a negligible antitumour effect throughout the experiment (Fig. 1, Table 1). After the first 4 weeks of treatment, the antitumour effect was maximum for regorafenib and less pronounced for sorafenib, sunitinib, bevacizumab and axitinib. In all the treated animal groups, tumour growth was resumed following drug withdrawal, although different growth
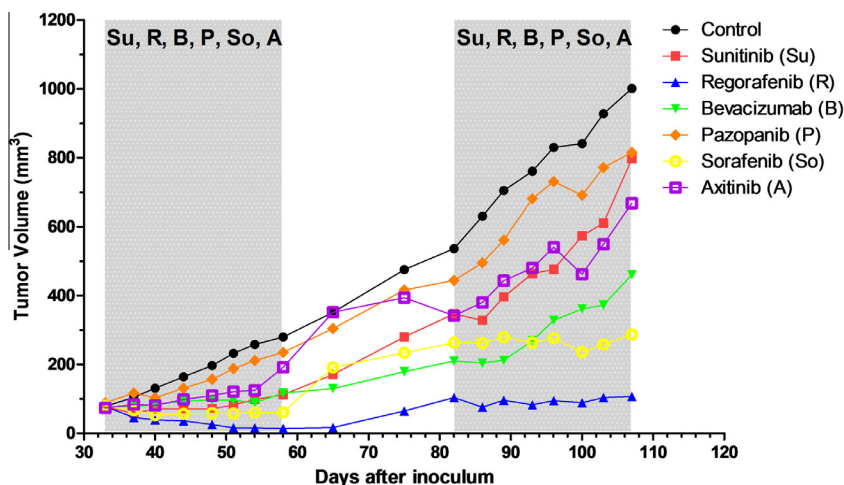
Fig. 1. Efficacy of pazopanib and other antiangionenic drugs against solitary fibrous tumour xenotransplanted into SCID mice. The treatment duration is indicated by the grey bar.

Table 1
Antitumour activity of pazopanib and other antiangiogenic drugs on solitary fibrous tumour xenograft.

Drug	Dose (mg/kg)	Schedule	Route	Max TVI% (day)
Pazopanib	100	qd × 5d/w × 4w × 2	p.o	21 (86)
Sorafenib	60	qd × 5d/w × 4w × 2	p.o	78 (58)[**]
Sunitinib	40	qd × 5d/w × 4w × 2	p.o	65 (51)[**]
Regorafenib	30	qd × 5d/w × 4w × 2	p.o	95 (65)[**]
Axitinib	25	2qd × 5d/w × 4w × 2	p.o	51 (54)[*]
Bevacizumab	4	q3-4d/w × 4w × 2	i.p	70 (89)[**]

[*] $p < 0.05$ and [**] $p < 0.01$ versus controls: Student's *t* test; TVI: tumour volume inhibition.

kinetics in the rest period were observed for the different compounds. In the case of regorafenib and sorafenib, the second run (4 weeks) of treatment, delivered after a 3-week rest, stabilised tumour volume for the duration of treatment (Fig. 1).

No sign of toxicity was registered, with the exception of regorafenib that caused a 10% body weight loss during the second run of treatment.

3.1.2. Pathologic evaluation of drug-treated xenograft

Pathologic evaluation was carried-out on tumour samples obtained after 2 h from the last drug administration, at the end of the first and of the second run of treatment. No histological changes were observed between treated and untreated tumours.

3.1.3. PDGFRB, VEGFR2 and ERK1/2 expression/activation

After the first 4 weeks of treatment sorafenib induced a decrease in PDGFRB expression/activation, regorafenib and especially axitinib induced a decrease in PDGFRB activation, while sunitinib, bevacizumab and pazopanib did not (Fig. 2A). Sunitinib, bevacizumab and regorafenib induced a weak decrease of VEGFR2 activation, while all the other treatments did not (Fig. 2B). The only drug that induced a decrease
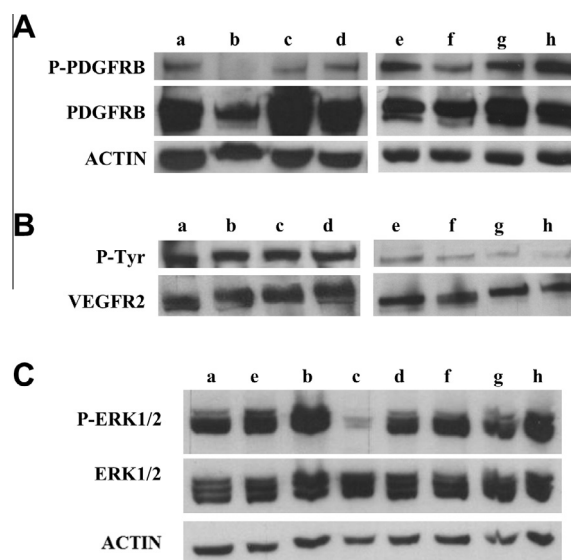

Fig. 2. Biochemical analyses of samples derived from mice treated with anti-angiogenic drugs. Panel A: Western blotting (WB) analysis of PDGFRB. Panel B: Immunoprecipitation/WB of VEGFR2. Panel C: WB analysis of ERK1/2. Mice were treated with sorafenib (b), axitinib (c), pazopanib (d), regorafenib (f), sunitinib (g), bevacizumab (h) for 4 weeks. No treated mice were used as control (a and e). The P-PDGFRB, P-Tyr, P-ERK1/2 panels identify the phosphorylated proteins; PDGFRB, VEGFR2, ERK1/2 panels indicate the expression of the corresponding proteins. Anti-actin antibody was used to normalise the results.

Table 2
Patient characteristics and clinical findings.

Patient ID	Sex	Primary tumour site	Prior chemotherapy (response)	Age at time of pazopanib (years)	Tumour type at time of pazopanib	Disease extension	Best Response Evaluation Criteria in Solid Tumour (RECIST) response	Best Choi response	PFS (mos)
1	F	Pelvis	Yes (NV)	53	MSFT	Abdomen, bone	SD	SD	5
2	F	Pleura	Yes (NV)	73	MSFT	Thoraco-abdominal wall, bone	SD	SD	3
3	M	Pleura	Yes (stable disease)	63	DSFT	Thoracic wall, lung	PD	PD	1
5	M	Pleura	Yes (no)	75	DSFT	Lung, soft tissue	PD	PD	2
6	F	Abdomen	Yes (no)	77	MSFT	Abdomen, lung	SD	PR	15
7	M	Kidney	Yes (yes)	33	DSFT	Lung, soft tissue, bone	PD	PD	2

F: female; M: male; NV: not valuable; MSFT: malignant solitary fibrous tumour; DSFT: dedifferentiated solitary fibrous tumour; SD: stable disease; PD: progressive disease; PR: partial response; PFS: progression free survival; mos: months.
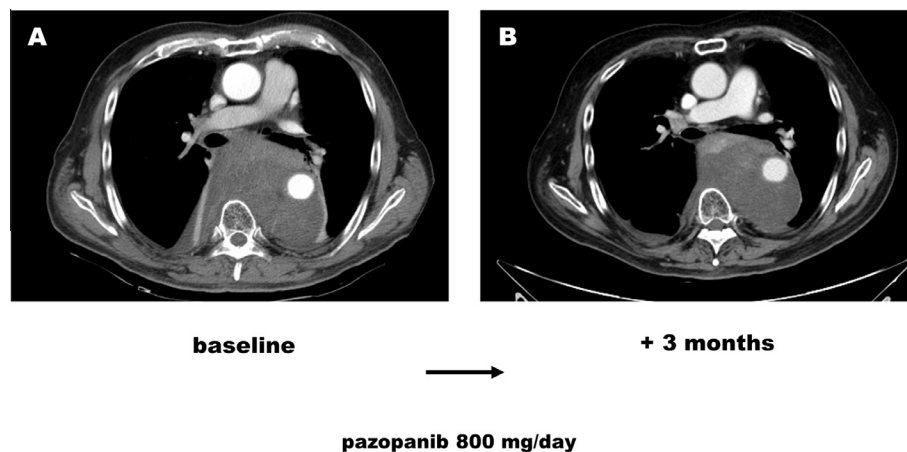

Fig. 3. Response to pazopanib. Computed tomography (CT) scan (arterial phase after contrast medium). Panel A shows a intrathoracic lesion from pleural solitary fibrous tumour at baseline. Three months after starting pazopanib a response was observed, marked by a decrease in tumour size and pleural effusion, and a decrease in tumour density (Panel B).

in ERK1/2 activation after one cycle of treatment was axitinib (Fig. 2C, line c) but this result was not confirmed by the analysis performed on the tumour samples excised after the second run (data not shown).

3.2. Patients

Six patients received pazopanib from May 2012 to October 2013. All cases completed their treatment (four progression; two toxicity) and were evaluable for response.

3.2.1. Patients

Table 2 summarises clinical findings.

Mean age was 62 years. PS was ⩽2 in all cases. All patients had progressed before starting treatment. Morphology was consistent with a diagnosis of malignant-SFT in three patients and dedifferentiated-SFT in the other three.

Median treatment duration was 3 months (range: 1–15). All patients started pazopanib 800 mg/day. Two

patients interrupted definitively their treatment due to toxicity (G3 liver toxicity: 1; G3 cardiac toxicity: 1). Toxicity resolved upon discontinuation.

3.2.2. Response

Best RECIST responses were three stable disease (SD) and three progressive disease (PD). According to Choi criteria best response was partial response (PR) in one, confirmed at 3 months, SD in two and PD in three (Fig. 3).

At a median 10-month follow-up, three patients are alive, three dead. Median PFS by RECIST was 3 months (range 1–15).

In one patient progressive under pazopanib, sunitinib 37.5 mg/day was started with response after 3 months (Fig. 4).

4. Discussion

In a mouse model of dedifferentiated-SFT, pazopanib showed the lowest antitumour activity (21%TVI), when
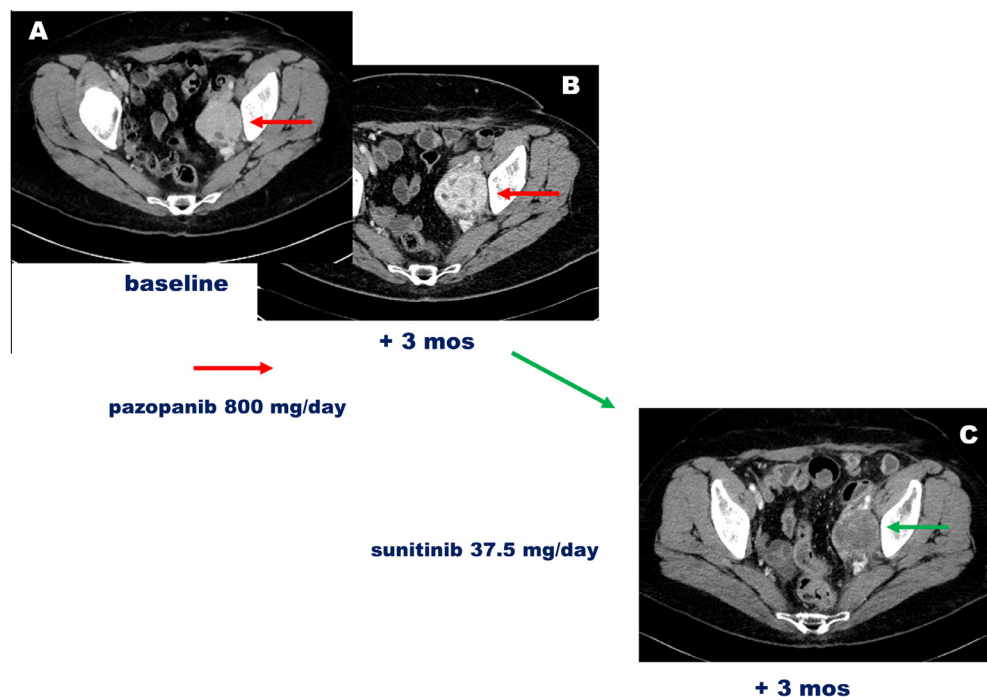
Fig. 4. Response to sunitinib after failure to pazopanib. Computed tomography (CT) scan (arterial phase after contrast medium). Panel A shows a pelvic lesion from pelvic solitary fibrous tumour at baseline. Three months after starting pazopanib a progression was observed, marked by an increase in tumour size and contrast uptake was observed (Panel B). On this basis pazopanib was interrupted and sunitinib was started with evidence of response 3 months later in terms of minor tumour shrinkage and hypodensity (Panel C).

compared to axitinib, bevacizumab, regorafenib, sorafenib and sunitinib, while regorafenib was the most active compound (95%TVI). Sorafenib, bevacizumab and sunitinib were also markedly active (78%, 70% and 65%TVI, respectively), whereas axitinib was marginally active (51%TVI). In a series of six patients with progressing metastatic SFT treated with pazopanib, the best responses according to RECIST were three SD and three PD, corresponding to one PR, two SD, three PD by Choi criteria, with a 3-month median PFS. All patients showing a tumour disease stabilisation under pazopanib were malignant-SFT, while those who progressed were high-grade dedifferentiated-SFT. Interestingly a response was subsequently obtained administering sunitinib in a patient who did not respond to pazopanib.

SFT represents a very rare disease and very few data are available on its sensitivity to pazopanib, that is the only antiangiogenic agent approved for STS treatment. Our preclinical results showed that pazopanib is less active compared to other antiangiogenics in a high-grade dedifferentiated-SFT mouse model [10]. By contrast regorafenib was found to be the most interesting compound. All the tested antiangiogenics showed a cytostatic effect. In all cases, indeed, tumour re-growth was observed after treatment discontinuation. This is consistent with the evidence that tumour samples after treatment with the different agents were made by viable cells in all cases. Of interest, among RTK inhibitors, pazopanib and axitinib were found to be less active than sunitinib, sorafenib and regorafenib. In particular,

pazopanib could obtain only a very modest decrease in tumour growth compared to control. A clear explanation for that is not yet available. The larger spectrum of kinase inhibition that marks sunitinib and especially sorafenib and regorafenib compared to pazopanib could make the difference. This hypothesis is corroborated by the evidence that, among the different antiangiogenics, only treatment reiteration (after a 3-week rest) with sorafenib and regorafenib, i.e. the two drugs with the largest spectrum of targets, was able to stabilise tumour volume. Biochemical analysis of PDGFRB, VEGFR2 and ERK1/2 after treatment showed that pazopanib did not switch-off any of the targets, consistently with its marginal activity. In contrast to what we expected, a decrease in kinase activation was not detected even in tumour samples which have responded to treatment. The presence of viable tumour cells in post-treatment samples even in tumours that significantly shrank strongly suggests the presence of resistant cells. We lack a definitive explanation for this observation and new experiments are in place to further investigate the different sensitivity of our SFT model to the antiangiogenics. We recently found that the antitumour effect of sunitinib in SFT patients is ascribable, at least in part, to antiangiogenic drug immunomodulating functions [18]. However, it is difficult to envisage such an effect in our patient-derived xenografts growing into immunodeficient hosts, such as SCID mice. To be noticed, the inhibitory effect of the different antiangiogenics on their target proteins is characterised by a different kinetics. As a consequence, the evaluation

of kinase phosphorylation status at a single time point, as we made in our experiment, could have prevented the possibility to compare properly the biochemical effects of the different compounds. We have started new experiments in tumour samples obtained at different intervals from mice treated with the different agents aimed at comparatively evaluating changes in the transcriptome as well as in the phosphorylation status of proteins belonging to relevant pathways.

The French group already reported on two SD out of six SFT patients treated with pazopanib (PFS 8 and 14 months, respectively) [9]. Our clinical data, even if retrospective and on a small number of patients, confirm that pazopanib had a modest activity in this sarcoma subtype and, interestingly, are in line with the preclinical results. No RECIST responses could be observed but in one patient the effect of pazopanib was marked by a minor (<30%) decrease in tumour size and by a decrease in tumour density, thus classifying for a PR by Choi criteria [11]. As already described for SFT treated with bevacizumab, sunitinib and sorafenib, Choi criteria [4–9], originally conceived for GIST receiving imatinib [11], differed from RECIST in assessing response to therapy. Of note, the patient with a Choi response had the best PFS (15 months). Our results seem to suggest a lower level of activity of pazopanib in SFT compared to sunitinib and bevacizumab plus temozolomide [5,6]. Median PFS of patients treated with pazopanib was 3 months, while a retrospective study on sunitinib in 31 SFT patients showed a Choi RR of about 50% with a 6-month median PFS [5]. Again, a Choi RR of 79% with a median PFS of 9.7 months was reported in SFT patients treated with bevacizumab and temozolomide [6]. Interestingly, patients who progressed under pazopanib had dedifferentiated-SFT, while the responsive case carried a malignant-SFT. This observation suggests that pazopanib might be more active in less aggressive cases, as already observed in SFT patients treated with sunitinib, and by contrast to what was observed with cytotoxic chemotherapy [19]. Worth noting, we obtained a response to sunitinib in a patient progressive to pazopanib consistently with the preclinical evidence of a non-superimposable activity of antiangiogenics in SFT.

Our results need to be confirmed prospectively. A European study on pazopanib in advanced SFT aimed at evaluating Choi response as primary end-point has just started. In addition, based on preclinical data showing that regorafenib is the most promising antiangiogenic agent, a prospective study on regorafenib in SFT is actually under discussion.

Funding

Disclosures

Conflict of interest statement

None declared.

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